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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,508	05/15/2007	Bengt Gustavsson	10400-000243/US	1311
30593 7590 05/27/2010 HARNESS, DICKEY & PIERCE, P.L.C. P.O. BOX 8910 RESTON, VA 20195				
EXAMINER				
ANDERSON, JAMES D				
ART UNIT		PAPER NUMBER		
1614				
MAIL DATE		DELIVERY MODE		
05/27/2010		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

**Application No.**

10/583,508

**Applicant(s)**

GUSTAVSSON ET AL.

**Examiner**

JAMES D. ANDERSON

**Art Unit**

1614

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 30 April 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.  
Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 8, 9, 11-18 and 20-23.  
Claim(s) withdrawn from consideration: \_\_\_\_\_.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

/James D Anderson/  
Primary Examiner, Art Unit 1614

Continuation of 11, does NOT place the application in condition for allowance because: Applicant's arguments and working examples are not persuasive to overcome the prima facie case of obviousness set forth by the Examiner over the prior art teachings of WO '660 in view of Hanauske and Niyikiza. The prior art recognized the benefit of administering methylene-tetrahydrofolate and tetrahydrofolate for modulating the antitumor effects and toxicities of anti-folate drugs such as 5-fluorouracil, methotrexate, trimetrexate, nitrous oxide, and dideoxytetrahydrofolic acid as evidenced by WO '660. The prior art also recognized the beneficial effects of co-administration of folic acid and pemetrexed. As evidenced by the cited prior art, folic acid was known to be metabolized in vivo to numerous biologically active metabolites, including, inter alia, methylene-tetrahydrofolate and tetrahydrofolate (see WO '660; Hanausake et al.; and Niyikiza et al.). Because in vivo administration of folic acid was known to ameliorate the toxicity of pemetrexed and possibly improve efficacy, the skilled artisan would have found it obvious to administer known in vivo metabolites of folic acid in combination with pemetrexed to ameliorate toxicity associated with pemetrexed therapy. Applicant's arguments have been carefully considered but remain unpersuasive. The Examiner is not persuaded that the effects of MTHF compared to folic acid are unexpected. As discussed in the previous Office Actions, folic acid is known to be metabolized in vivo to active metabolites such as MTHF. As such, the fact that direct administration of MTHF is more efficacious than administration of folic acid is not seen by the Examiner to be unexpected in view of the fact that no metabolism of MTHF need occur for it to be pharmacologically active. Further, because pemetrexed inhibits multiple enzymes responsible for metabolism of folic acid, it would be expected that administration of folic acid and pemetrexed would be less effective than direct administration of an active metabolite of folic acid such as MTHF.